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THE DYNAMICS OF A NONLINEAR MODEL OF SIGNAL TRANSDUCTION IN HUMAN UNDER IMPULSIVE DEPRESSANT DRUG TREATMENT

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ABSTRACT. A mathematical model of the signal transduction process, involving hormone coupled receptors and an inhibiting enzyme, under impulsive depressant treatment, is proposed and analyzed. We show that there is a stable periodic solution, at the vanishing density of the ligand bound receptors on the cell membrane and plasmalemma, when the impulsive period is less than some critical value. The conditions for permanence of the system are then given. Finally, it is shown that as the impulsive period increases beyond a certain critical value, the emergence of stable positive periodic solution may be observed under appropriate conditions on the system parameters.

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1. INTRODUCTION

Many systems in nature are impulsive, in which a system variable experiences a quick jump, or an abrupt drop, at equal time intervals (periodic impulses). For example, a predator prey system with periodic harvesting, or crop dusting. A signaling process among living cells could experience signal pulses that stimulate or inhibit certain responses that may become difficult to control. Therefore, the stability and permanence of such systems are of great interest in clinical applications.

In this paper, a system of nonlinear differential equations describing the signal transduction process in human, under impulsive treatment of depressant drugs, is considered. The model is based on that proposed by Iglesias [1] in 2003, involving membrane bound receptors which, on binding with the signaling hormone or ligand, relay external messages to a series of internal reactants, which in turn trigger key cellular functions, such as secretion of the secondary hormone cAMP (cyclic adenosine mono-phosphate), a process that is also regulated by an inhibitor. We modified, in [2] and [3], the model in [1] by allowing some transport of the hormone coupled receptors across the cell membrane to take place to a certain extent. The model also takes into

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account the amplification effect that the secondary hormone exerts on the primary external signals. In [4], measurements of intracellular cAMP were made using Fisher rat thyroid cells expressing type II vasopressin receptors. This experimental data was then fitted with the cAMP level calculated from the model in [2], observing that the simulated curve fits the experimental data rather well although there are some discrepancies that need further investigations. It also suggests that other physical factors may be at play which we need to take into account.

Abnormalities of signal transduction pathways have been linked to the development of many serious disorders, such as cancer which derives from a cell that has lost the ability to respond normally to controls from outside, or inside, the cell [5]. Many tumors produce ectopical amounts of biologically active hormones that create dysfunctions of the signal transduction process leading to abnormal effects. Hormones and antihormones are used to treat certain types of cancer. Many cancers are related to the status of hormones in the body. An avenue of cancer treatment is to utilize appropriate hormones as chemotherapeutic agents. For example, tamoxifen can interfere with the offensive effects of estrogen, resulting in the inhibition of cellular growth of the tumor. For another example, Vasopressin has been proposed for its potential effect of slowing down the flow of blood that tumors depend on for growth [6].

We incorporate such periodic drug treatments or external signals by using the following impulsive system.

$$\frac{dx_1}{dt} = -a_1x_1 - \frac{b_1x_1}{b_2+x_1^2} + \frac{b_3x_1}{b_4x_1+x_2} \equiv f_1(x_1,x_2), \quad t \neq kT \tag{1.1}$$

$$\frac{dx_2}{dt} = -a_2x_2 + a_3x_1 \equiv f_2(x_1,x_2), \quad t \neq kT \tag{1.2}$$

$$\left.\begin{aligned} \triangle x_1 &= -px_1 \\ \triangle x_2 &= \mu \end{aligned}\right\} \quad t = kT, \tag{1.3}$$

$k \in \mathbb{Z}_+$, where

$$\triangle x_i(t) = x_i(t^+) - x_i(t), \quad i = 1, 2,$$

T is the period of the impulsive effect of drug treatments, $x_1(t)$ is the density above the basal level of ligand coupled receptors (LCR) on the cell membrane, $x_2(t)$ is that of the inhibiting agent, a_1 is the specific removal rate of x_1 by natural means, a_2 is the specific removal rate of x_2 by natural means, and a_3 is the rate of production of x_2 per unit of the hormone coupled receptors x_1.

The second term on the right of equation (1.1) accounts for the internalization of x_2 across the cell membrane which is assumed here to saturate as x_1 becomes high. The third term accounts for the amplification effect of the secondary hormone on the first messenger's signaling strength. In [1], this effect was assumed to vary directly as the level of the secondary hormone $C(t)$ at any time t, the production rate of which was assumed to vary as the square of the amount R of activated regulators, namely, the activated units of adenylate cyclase (AD). Assuming that cAMP equilibrates relatively quickly, they then arrived at an expression for $C(t)$ of the form

$$C(t) = \tilde{b}_5 R^2 + k_0 \tag{1.4}$$

where $\tilde{b}_5$ is a positive constant, and k_0 corresponds to the zero order secretion rate of cAMP. The activated units of AD is related to the signaling strength S, and the inhibiting agents I as:

$$R = \frac{\tilde{k} S}{b_4 S + I} \tag{1.5}$$

so that, according to [1] and [2], the level of cAMP at any time t may be expressed in the form

$$C(t) = \frac{b_5 S^2}{(b_4 S + I)^2} + k_0 \tag{1.6}$$

where $b_5 = \tilde{k}\tilde{b}_5$. Details of the derivation may be found in [1] and [2].

In this paper, the primary hormone signaling strength is reflected in the density x_1 of LCR above the basal level, while the inhibiting strength is reflected by x_2. We consider that it may be more reasonable to assume that the production rate of cAMP varies as the current level of the activated units of AD. Therefore, in place of (1.6), we arrive at

$$C(t) = \frac{b_5 x_1}{b_4 x_1 + x_2} \tag{1.7}$$

in which we have also assumed that the zero order secretion rate of the secondary hormone (cAMP) is negligible at the basal level of LCR ($x_1 = 0$), so that $k_0 = 0$. This then leads to the third term on the right of (1.1) where $b_3 = k b_5$, k being a constant of variation.

Equation (1.3) accounts for the depressive effect of the periodic drug treatment which reduces the stimulating strength of the first messenger resulting in the decrease in LCR by the fraction $p, 0 < p < 1$, while the inhibiting effect is increased by the amount $\mu, \mu > 0$.

In Section 2, we give some lemmas which are useful for proving our main results. In Section 3, the conditions which assure the locally asymptotic stability of the periodic solution at the vanishing level of LCR are given. Permanence is then shown to be possible provided the treatment period T is sufficiently large. Finally, the existence and stability of positive periodic solution to the system (1.1)–(1.3) is investigated in Section 4. The last section then contains numerical results and concluding remarks.

2. PRELIMINARIES

In order to prove our main results, we need to give some lemmas which need the following definition [7].

Definition 2.1. Let $V : \mathbb{R}_+ \times \mathbb{R}^2_+ \to \mathbb{R}_T$, where $\mathbb{R}_+ = [0, \infty)$, be continuous in $(nT, (n+1)T] \times \mathbb{R}^2_+$ and for each $x \in \mathbb{R}^2_+$, $n \in \mathbb{Z}_+$, $\lim_{(t,y)\to(nT^+,x)} V(t, y) = V(nT^+, x)$ exists. Also, let V be locally Lipschitzian in x. Then, for $(t, x) \in (nT, (n+1)T] \times \mathbb{R}^2_+$, the upper right derivative of $V(t, x)$ with respect to the impulsive differential system (1.1)–(1.3) is defined as

$$D^+V(t, x) = \limsup_{h\to 0^+} \frac{1}{h}[V(t + h, x + hf(t, x)) - V(t, x)],$$

where $f = (f_1, f_2)$.

The solution $x(t) = (x_1(t), x_2(t))$ of (1.1)–(1.3) is a piecewise continuous function, $x : \mathbb{R}_T \to \mathbb{R}^2_+$ continuous on $(nT, (n+1)T)$, $n \in \mathbb{Z}_+$, and $x(nT^+) = \lim_{t\to nT^+} x(t)$ exists. Thus, the global existence and uniqueness of solutions of (1.1)–(1.3) are assured by the smoothness properties of f.

Since $\frac{dx_1}{dt} = 0$ whenever $x_1(t) = 0$, $t \neq nT$, $\frac{dx_2}{dt} > 0$ whenever $x_2(t) = 0$, $t \neq nT$, and $x_1(nT^+) = (1 - p)x_1(nT)$, $0 < p < 1$, $x_2(nT^+) = x_2(nT) + \mu$, $\mu > 0$, we have the following lemma.

Lemma 2.2. *Suppose $x(t) = (x_1, x_2)$ is a solution of (1.1)–(1.3) with $x_i(0^+) \geq 0$, $i = 1, 2$. Then, $x_i(t) > 0$, $i = 1, 2$, for $t \geq 0$ if $x_i(0^+) > 0$, $i = 1, 2$.*

Next, we show that all solutions of (1.1)–(1.3) are uniformly ultimately bounded.

Lemma 2.3. *There exists a constant $M > 0$ such that $x_i \leq M$, $i = 1, 2$, for each solution $x(t) = (x_1, x_2)$ of (1.1)–(1.3) with all t sufficiently large if*

$$a_1 > a_3 \tag{2.1}$$

Proof. Letting $\boldsymbol{V}(t) = V(t, x(t)) = x_1(t) + x_2(t)$, and choosing

$$c = \min(a_1 - a_3, a_2)$$

which is positive, we have when $t \neq kT$ that

$$\begin{aligned} D^+\boldsymbol{V}(t) + c\boldsymbol{V} &= -a_1x_1 - \frac{b_1x_1}{b_2 + x_1^2} + \frac{b_3x_1}{b_4x_1 + x_2} - a_2x_2 + a_3x_1 + cx_1 + cx_2 \\ &\leq (-a_1 + c + a_3)x_1 + b + (-a_2 + c)x_2 \leq b \end{aligned}$$

where $b = \frac{b_3}{b_4}$. That is, when $t \neq kT$, $D^+\boldsymbol{V} \leq -cv + b$.

When $t = t_k = kT$,

$$\boldsymbol{V}(kT^+) = x_1(kT^+) + x_2(kT^+) = x_1(t_k) - px_1 + x_2(t_k) + \mu \leq \boldsymbol{V}(t_k) + \mu$$

By Lemma 2.2 in [5], for $t \in (kT, (k+1)T]$ we have

$$\begin{aligned} \boldsymbol{V}(t) \leq\ & \boldsymbol{V}(0)e^{-ct} + b\int_0^t e^{-c(t-s)}ds + \mu \sum_{0<t_k<t} e^{-\int_{t_k}^{t} c\,d\tau} \\ =\ & \boldsymbol{V}(0)e^{-ct} + \frac{b}{c}(1-e^{-ct}) + \mu\left[\frac{e^{-c(t-T)} - e^{-c(t-t_{k+1})}}{1-e^{cT}}\right] \\ <\ & \frac{b}{c} + \frac{\mu e^{cT}}{e^{cT}-1} \qquad \text{as } t \to \infty. \end{aligned}$$

So, $\boldsymbol{V}(t)$ is uniformly ultimately bounded. Hence, by the definition of $\boldsymbol{V}$, there is an $M > 0$ such that $x_i \leq M$, $i = 1, 2$. □

Finally, we consider the following reduced system

$$\frac{dx_2}{dt} = -a_2x_2, \quad t \neq kT, \tag{2.2}$$

$$x_2(kT^+) = x_2(kT) + \mu, \quad t = kT, \tag{2.3}$$

$$x_2(0^+) = x_{2_0} \tag{2.4}$$

We see that the following function

$$\tilde{x}_2(t) = \frac{\mu \exp(-a_2(t-kT))}{1-\exp(-a_2T)},$$

for $t \in (kT, (k+1)T]$, $k \in \mathbb{Z}_+$, is a positive solution of the system (2.2)–(2.4) such that

$$\tilde{x}_2(0^+) = \frac{\mu}{1-e^{-a_2T}}.$$

Thus, the solution of (2.2)–(2.4) is $x_2(t) = \left(x_{2_0} - \frac{\mu}{1-e^{-a_2T}}\right)e^{-a_2t} + \tilde{x}_2(t)$, $t \in (kT, (k+1)T)$ and therefore we have the following Lemma.

Lemma 2.4. *The system* (2.2)–(2.4) *has a positive periodic solution* $\tilde{x}_2(t)$*, and for every solution* $x_2(t)$ *of* (2.2)–(2.4)*, we have* $x_2(t) \to \tilde{x}_2(t)$ *as* $t \to \infty$*.*

Hence, system (1.1)–(1.3) has a periodic solution at the vanishing level of LCR:

$$(0, \tilde{x}_2(t)) = \left(0, \frac{\mu e^{-a_2(t-kT)}}{1-e^{-a_2T}}\right) \tag{2.5}$$

for $kT < t \leq (k+1)T$, and $\tilde{x}_2(kT^+) = \tilde{x}_2(0^+) = \frac{\mu}{1-e^{-a_2T}}$, $k \in \mathbb{Z}_+$.

3. VANISHING STIMULUS AND PERMANENCE

We first give the conditions that guarantee the locally asymptotic stability of the periodic solution $(0, \tilde{x}_2(t))$ at the point of vanishing stimulus.

Theorem 3.1. *Let $x(t)$ be any solution of (1.1)–(1.3). Then, $(0, \tilde{x}_2(t))$ is locally asymptotically stable if*

$$T < T_{\max} \tag{3.1}$$

with

$$\frac{4\mu b_3}{a_2}\sinh^2\frac{a_2 T_{\max}}{2} = \left(a_1 + \frac{b_1}{b_2}\right)T_{\max} + \ln\frac{1}{1-p} \tag{3.2}$$

Proof. Consider a small amplitude perturbation of $(0, \tilde{x}_2(t))$:

$$x_1(t) = u(t)$$

$$x_2(t) = \tilde{x}_2 + v(t)$$

We may write

$$\begin{pmatrix} u(t) \\ v(t) \end{pmatrix} = \Phi(t)\begin{pmatrix} u(0) \\ v(0) \end{pmatrix}, \quad 0 < t < T$$

where Φ satisfies

$$\frac{d\Phi}{dt} = \begin{pmatrix} -a_1 - \dfrac{b_1}{b_2} + \dfrac{b_3}{\tilde{x}_2} & 0 \\ a_3 & -a_2 \end{pmatrix}\Phi$$

and $\Phi(0) = I$, the identity matrix. Hence, the fundamental solution matrix is

$$\Phi = \begin{pmatrix} \exp\int_0^t\left(-a_1 - \dfrac{b_1}{b_2} + \dfrac{b_3}{\tilde{x}_2}\right)ds & 0 \\ * & \exp\int_0^t(-a_2)ds \end{pmatrix}$$

for which it is not necessary to find the exact expression for (*) since it is not required in the following analysis.

Linearization of (1.3) gives

$$\begin{pmatrix} u(kT^+) \\ v(kT^+) \end{pmatrix} = \begin{pmatrix} 1-p & 0 \\ 0 & 1 \end{pmatrix}\begin{pmatrix} u(kT) \\ v(kT) \end{pmatrix}$$

The stability of the periodic solution $(0, \tilde{x}_2(t))$ is determined by the eigenvalues of

$$M_0 = \begin{pmatrix} 1-p & 0 \\ 0 & 1 \end{pmatrix}\Phi(T)$$

which are

$$v_1 = (1-p)e^{\int_0^T\left(-a_1 - \frac{b_1}{b_2} + \frac{b_3}{\tilde{x}_2}\right)ds} \tag{3.3}$$

and

$$v_2 = e^{-a_2 T} < 1$$

According to the Floquet theory, $(0, \tilde{x}_2(t))$ will be locally stable if $|v_1| < 1$. We observe that

$$\begin{aligned}\int_0^T \frac{1}{\tilde{x}_2} ds &= (1 - e^{-a_2 T})\mu \int_0^T e^{a_2 s} ds \\ &= \frac{\mu}{a_2}(1 - e^{-a_2 T})(e^{a_2 T} - 1) \\ &= \frac{\mu}{a_2}(e^{a_2 T} - 1)/e^{a_2 T} \\ &= \frac{\mu}{a_2}\left(e^{\frac{a_2 T}{2}} - e^{\frac{-a_2 T}{2}}\right)^2 \\ &= \frac{4\mu}{a_2}\sinh^2(a_2 T/2)\end{aligned}$$

Hence, $|v_1| < 1$ if

$$b_3 \cdot \frac{4\mu}{a_2}\sinh^2\frac{a_2 T}{2} < \left(a_1 + \frac{b_1}{b_2}\right)T + \ln\frac{1}{1-p} \tag{3.4}$$

Letting $\Im_1(T)$ be the function on the left of (3.2), and $\Im_2(T)$ be that on its right, then we see that $\Im_1(0) - \Im_2(0) < 0$, while $\Im_1(T) - \Im_2(T) \to \infty$ as $T \to \infty$. Since $\Im_1 - \Im_2$ is increasing for $T > 0$, there must be one and only one value $T = T_{\max}$ at which $\Im_1(T_{\max}) = \Im_2(T_{\max})$ and $\Im_1(T) < \Im_2(T)$ for all $T < T_{\max}$. The proof is complete. □

We next investigate the permanence of (1.1)–(1.3) by first giving the following definition.

Definition 3.2. System (1.1)–(1.3) is said to be permanent if there are constants $m, M > 0$ (independent of initial values) and a finite time t_0 such that for all solutions $x(t)$ with all initial values $x_i(0^+) > 0$, $m \le x_i(t) \le M$ for all $t \ge t_0$, $i = 1, 2$. Here, t_0 may depend on the initial values.

Theorem 3.3. *The system* (1.1)–(1.3) *is permanent if* (2.1) *holds and*

$$T > T_{\max} \tag{3.5}$$

Proof. Suppose $x(t) = (x_1, x_2)$ is a solution of (1.1)–(1.3) with $x_i(0) > 0$, $i = 1, 2$. By Lemma 2.2, there is an $M > 0$ such that $x_i \le M$, for t large enough.

From (1.2), we know

$$\frac{dx_2}{dt} \ge -a_2 x_2, \quad t \ne kT$$

$$x_2(t^+) = x_2(t) + \mu, \quad t = kT$$

and we have

$$x_2(t) > \tilde{x}_2(t) - \varepsilon$$

for all t large enough and some $\varepsilon > 0$, so that

$$x_2(t) \geq \frac{\mu e^{-a_2 T}}{1 - e^{-a_2 T}} - \varepsilon \equiv m_2$$

for t large enough. Thus, we only need to find an $m_1 > 0$ such that

$$x_1(t) \geq m_1, \quad \text{for } t \text{ large enough.}$$

Step 1 From the arguments in Theorem 3.1, we see that if $T > T_{\max}$, then

$$(1-p)\exp\int_{kT}^{(k+1)T}\left(-a_1 - \frac{b_1}{b_2} + \frac{b_3}{\tilde{x}_2}\right)dt > 1 \tag{3.6}$$

where

$$\tilde{x}_2 = \frac{\mu\exp(-a_2(t-kT))}{1-\exp(-a_2 T)}$$

By continuity of the integral in (3.6), if $m_3 > 0$ and $\varepsilon_1 > 0$ are small enough, then

$$\eta \equiv (1-p)\exp\int_{kT}^{(k+1)T}\left(-a_1 - \frac{b_1}{b_2} + \frac{b_3}{b_4 m_3 + \tilde{z} + \varepsilon_1}\right)dt > 1 \tag{3.7}$$

also, where $\tilde{z} = \tilde{x}_2 + \frac{a_3 m_3}{a_2}$.

We will prove that $x_1(t) < m_3$ cannot hold for all $t \geq 0$. Otherwise,

$$\frac{dx_2}{dt} = -a_2 x_2 + a_3 x_1 \leq -a_2 x_2 + a_3 m_{3,}, \quad t \neq kT$$

$$x_2(t^+) = x_2(t) + \mu, \quad t = kT$$

if $x_1(t) \geq 0$

We then obtain $x_2(t) \leq z(t)$ and $z(t) \to \tilde{z}(t)$, $t \to \infty$, where $z(t)$ is the solution of

$$\begin{cases} \dfrac{dz}{dt} = -a_2 z(t) + a_3 m_3 & , \quad t \neq kT \\ z(t^+) = z(t) + \mu & , \quad t \neq kT \\ z(0^+) = x_2(0^+) \end{cases} \tag{3.8}$$

and

$$\tilde{z}(t) = \frac{\mu\exp(-a_2(t-kT))}{1-\exp(-a_2 T)} + \frac{a_3}{a_2}m_3, \quad t \in (kT, (k+1)T]$$

Therefore, there exists a $t_1 > 0$ such that

$$x_2(t) < z(t) < \tilde{z}(t) + \varepsilon_1$$

and

$$\begin{aligned} \frac{dx_1}{dt} &\geq x_1(t)\left(-a_1 - \frac{b_1}{b_2} + \frac{b_3}{b_3 m_3 + \tilde{z} + \varepsilon_1}\right) \quad , \quad t \neq kT \\ x_1(t^+) &= (1-p)x_1(t) \qquad\qquad\qquad\qquad\quad , \quad t \neq kT \end{aligned} \tag{3.9}$$

for $t \geq t_1$. Let $N \in \mathbb{Z}_+$ and $NT \geq t_1$.

Integrating (3.9) over $(kT,(k+1)T, k \geq N$, we have

$$x_1((k+1)T) \geq x_1(kT)(1-p)\exp\left(\int_{kT}^{(k+1)T}\left(-a_1-\frac{b_1}{b_2}+\frac{b_3}{b_4 m_3+\tilde{z}+\varepsilon_1}\right)dt\right)$$
$$= x_1(kT)\eta$$

then

$$x_1((N+k)T) \geq x_1(NT)\eta^k \to \infty \quad \text{as } k\to\infty$$

which is a contradiction to the boundedness of $x_1(t)$. Hence, there is a $t_c > t_1$ such that

$$x_1(t_c) \geq m_3$$

Step 2 If $x_1(t) \geq m_3$, for all $t > t_c$, then our job is done. Otherwise, there is a $t' > t_c$ such that

$$x_1(t') < m_3$$

Then, let $t^* = \inf\limits_{t>t_c}\{t : x_1(t) < m_3\}$, and there are two possible cases for t^*.

Case 2.1 $t^* = k_1T$, for some $k_1 \in \mathbb{Z}_+$. Then

$$x_1(t) \geq m_3 \quad \text{ for } t \in [t_c, t^*]$$

and

$$m_3 > x_1(t^{*+}) = (1-p)x_1(t^*) \geq m_3(1-p)$$

Choose $k_2, k_3 \in \mathbb{Z}_+$ such that

$$k_2T > T_1$$
$$(1-p)^{k_2}\exp(k_2\eta_1 T)\eta^{k_3} > (1-p)^{k_2}\exp((k_2+1)\eta_1 T)\eta^{k_3} > 1$$

where $\eta_1 = -a_1 - \frac{b_1}{b_2} + \frac{b_3}{M(1+b_4)} < 0$

Let $T' = k_2T + k_3T$. We claim that there must be a $t_2 \in (t^*, t^* + T']$ such that

$$x_1(t_2) > m_3$$

Otherwise (3.9) holds for $t^* + k_2T \leq t \leq t^* + T'$. So, as in Step 1, we have

$$x_1(t^*+T') \geq x_1(t^*+k_2T)\eta^{n_3} \tag{3.10}$$

On the other hand, for $t \in [t^*, t^* + k_2T]$, we have from (1.1) that

$$\begin{aligned} \frac{dx_1}{dt} &\geq x_1(t)\left(-a_1-\frac{b_1}{b_2}+\frac{b_3}{M(1+b_4)}\right) \quad , \quad t \neq kT \\ x_1(t^+) &= (1-p)x_1(t) \qquad\qquad\qquad\qquad , \quad t \neq kT \end{aligned} \tag{3.11}$$

Integrating (3.11) over $[t^*, t^* + k_2T]$, we have

$$x_1(t^*+k_2T) \geq m_3(1-p)^{k_2}\exp(k_2\eta_1 T)$$

Substituting into (3.10), we have

$$x_1(t^*+T') \geq m_3(1-p)^{k_2}\exp(k_2\eta_1 T)\eta^{k_3} > m_3$$

which is a contradiction.

Hence, there is a $t_2 \in (t^*, t^* + T']$ such that

$$x_1(t_2) > m_3$$

So, let $\tilde{t} = \inf_{t>t^*}\{t : x_1(t) > m_3\}$. Then, for $t \in (t^*, \tilde{t})$, $x_1(t) \leq m_3$ and $x_1(\tilde{t}) = m_3$ since $x_1(t)$ is left continuous and

$$x_1(t^+) = (1-p)x_1(t) \leq x_1(t)$$

when $t = kT$.

For $t \in (t^*, \tilde{t})$ suppose $t \in (t^* + (l-1)T, t^* + lT]$, $l \in \mathbb{Z}_+$ and $l \leq k_2 + k_3$. From (3.10), we have

$$\begin{aligned} x_1(t) &\geq x_1(t^{*+})(1-p)^{l-1}\exp((l-1)\eta_1 T)\exp(\eta_1(t - (t^* + (l-1)T)) \\ &\geq m_3(1-p)^l \exp(l\eta_1 T) \\ &\geq m_3(1-p)^{k_2+k_3}\exp((k_2+k_3)\eta_1 T) \equiv m_1' \end{aligned}$$

So, we have $x_1(t) \geq m_1'$ for $t \in (t^*, \tilde{t})$ and $x_1(\tilde{t}) \geq m_3$. We can repeat the argument for $t > \tilde{t}$ to obtain the result that $x_1(t) \geq m_1 > 0$ for t large enough.

Case 2.2 $t^* \neq kT$, for all $k \in \mathbb{Z}_+$. Then,

$$x_1(t) \geq m_3 \quad \text{for } t \in (t_1, t^*)$$

and

$$x_1(t^*) = m_3.$$

Suppose $t^* \in (k_1'T, (k_1'+1)T)$ for some $k_1' \in \mathbb{Z}_+$. There are 2 possible cases for $t \in (t^*, (k_1'+1)T)$.

Case 2.2 a) $x_1(t) \leq m_3$ for all $t \in (t^*, (k_1'+1)T)$. We claim that there must be a $t_2' \in [(n_1'+1)T, (n_1'+1)T + T']$ such that $x_1(t_2') > m_3$. Otherwise, similarly to Case 2.1, we get

$$x_1((k_1'+1+k_2+k_3)T) \geq x_1((k_1'+1+k_2)T)\eta^{n_3}$$

On the other hand, for $t \in (t^*, (k_1'+1)T)$, (3.11) holds on $[t^*, (k_1'+1+k_2+k_3)T]$, and $x_1(t) \leq m_3$, so that we have

$$x_1((k_1'+1+k_2)T \geq m_3(1-p)^{k_2}\exp((k_2+1)\eta_1 T)$$

Thus,

$$x_1((k_1'+1+k_2+k_3)T) \geq m_3(1-p)^{k_2}\exp((k_2+1)\eta_1 T)\eta^{n_3} > m_3,$$

a contradiction.

Let $\bar{t} = \inf_{t>t^*}\{t : x_1(t) > m_3\}$. Then,

$$x_1(t) \leq m_3 \quad \text{for } t \in (t^*, \bar{t})$$

and

$$x_1(\bar{t}) = m_3.$$

For $t \in (t^*, \bar{t})$, suppose $t \in (k_1'T + (l'-1)T, k_1'T + l'T]$, for some $l' \in \mathbb{Z}_+$, $l' \leq 1 + k_2 + k_3$. Then, we have

$$\begin{aligned} x_1(t) &\geq m_3(1-p)^{l'-1}\exp(l'\eta_1 T) \\ &\geq m_3(1-p)^{k_2+k_3}\exp((k_2+k_3+1)\eta_1 T) \equiv m_1 \end{aligned}$$

So, $x_1(t) \geq m_1$ for $t \in (t^*, \bar{t})$. The same arguments can be applied for $t > \bar{t}$, since $x_1(\bar{t}) \geq m_3$. We thus get $x_1(t) \geq m_1 > 0$ for all t large enough.

Case 2.2 b) There exists a $t \in (t^*, (k_1+1)T)$ such that $x_1(t) > m_3$.

Let $\hat{t} = \inf\limits_{t > t^*}\{t : x_1(t) > m_3\}$. Then,

$$x_1(t) \leq m_3 \quad \text{for } t \in (t^*, \hat{t})$$

and

$$x_1(\hat{t}) = m_3.$$

For $t \in (t^*, \hat{t})$, (3.11) holds and integrating (3.11) on $(t^*, \hat{t})$, we have

$$x_1(t) \geq x_1(t^*)\exp(\eta_1(t - t^*)) \geq m_3 \exp(\eta_1 T) > m_1$$

Using the fact that $x_1(\hat{t}) \geq m_3$, we may apply the above argument again for $t > \hat{t}$.

Hence, we obtain $x_1(t) \geq m_1 > 0$ for all $t \geq t_c$, and the proof is complete. □

We now investigate the possibility of bifurcation of positive periodic solution to the system (1.1)–(1.3) near $(0, \tilde{x}_2, (t))$.

For this purpose, it is more convenient to exchange x_1 and x_2 and let $\tau_0 = T_{\max}$ as given in (3.2). The system (1.1)–(1.3) is now written as

$$\frac{dx_1}{dt} = -a_2x_1 + a_3x_2, \quad t \neq k\tau \tag{3.12}$$

$$\frac{dx_2}{dt} = -a_1x_2 - \frac{b_1x_2}{b_2 + x_2^2} + \frac{b_3x_2}{b_4x_2 + x_1}, \quad t \neq k\tau \tag{3.13}$$

$$\left.\begin{aligned} \triangle x_1(t) &= \mu \\ \triangle x_2(t) &= -px_2(t) \end{aligned}\right\} \quad t = k\tau \tag{3.14}$$

By Theorem 2 of [8], we then have the following result.

Theorem 3.4. *The system* (1.1)–(1.3) *has a positive periodic solution which is supercritical provided* (2.1) *and* (3.5) *hold.*

Proof. Relying on the notations used in [8], we have

$$\begin{aligned}
F_1(x_1,x_2) &\equiv -a_2x_1 + a_3x_2 \\
F_2(x_1,x_2) &\equiv -a_2x_2 - \frac{b_1x_2}{b_2+x_2^2} + \frac{b_3x_2}{b_4x_2+x_1} \\
\Theta_1(x_1,x_2) &\equiv x_1 + \mu, \\
\Theta_2(x_1,x_2) &\equiv (1-p)x_2 \\
\zeta(t) &\equiv (\tilde{x}_2(t),0)^T \\
x_0 &\equiv (\tilde{x}_2(\tau_0),0)^T.
\end{aligned}$$

We then can determine the relevant quantities as follows.

$$\frac{\partial^2\Phi_2}{\partial x_1\partial x_2}(\tau_0,x_0) = \int_0^{\tau_0} \exp\left(\int_u^t \frac{\partial F_2}{\partial x_2}ds\right)\frac{\partial^2 F_2}{\partial x_1\partial x_2}\exp\left(\int_0^u \frac{\partial F_2}{\partial x_2}ds\right)du\Bigg]_{(\tau_0,x_0)} < 0$$

since $\frac{\partial^2 F_2}{\partial x_1\partial x_2}\Big]_{(\tau_0,x_0)} = \frac{-b_3}{\tilde{x}_2^2} < 0$.

Since $\frac{\partial^2\Theta_2}{\partial x_1\partial x_2} = 0$, we have

$$B = -\frac{\partial\Theta_2}{\partial x_2}\left(\frac{\partial^2\Phi_2}{\partial\tau\partial x_2} + \frac{\partial^2\Phi_2}{\partial x_1\partial x_2}\cdot\frac{1}{a_0'}\frac{\partial\Theta_1}{\partial x_1}\cdot\frac{\partial\Phi_1}{\partial\tau}\right)\Bigg]_{(\tau_0,x_0)}.$$

Noting that, if (3.5) holds,

$$\begin{aligned}
a_0' = 1 - \frac{\partial\Theta_1}{\partial x_1} - \frac{\partial\Phi_1}{\partial x_1}\Bigg]_{(\tau_0,x_0)} &> 0 \\
\frac{\partial\Phi_1}{\partial x_1}\Bigg]_{(\tau_0,x_0)} = \exp\int_0^t \frac{\partial F_1}{\partial x_1}ds\Bigg]_{(\tau_0,x_0)} &> 0 \\
\frac{\partial\Phi_1}{\partial\tau}\Bigg]_{\tau_0} = -\frac{a_2\mu\exp(-a_2\tau_0)}{1-\exp(-a_2\tau_0)} &< 0 \\
\frac{\partial^2\Phi_2}{\partial\tau\partial x_2}\Bigg]_{(\tau_0,x_0)} = -\frac{\partial F_2}{\partial x_2}\exp\int_0^t \frac{\partial F_2}{\partial x_2}ds\Bigg]_{(\tau_0,x_0)} & \\
= \left(-a_1 - \frac{b_1}{b_2} + \frac{b_3}{\tilde{x}_2}\right)\exp\int_0^t \frac{\partial F_2}{\partial x_2}ds\Bigg]_{(\tau_0,x_0)} &> 0.
\end{aligned}$$

We conclude that

$$B < 0$$

Next, since Θ_1 and Θ_2 are linear we have [8]

$$C = \frac{\partial\Theta_2}{\partial x_2}\left(2\frac{b_0'}{a_0'}\frac{\partial^2\Phi_2}{\partial x_1\partial x_2} - \frac{\partial^2\Phi_2}{\partial x_2^2}\right)\Bigg]_{(\tau_0,x_0)}$$

Referring to [8] for the definitions of the partial derivative terms appearing above, we specifically have

$$b_0' = -\left(\frac{\partial\Theta_1}{\partial x_1}\frac{\partial\Phi_1}{\partial x_2} + \frac{\partial\Theta_1}{\partial x_2}\frac{\partial\Phi_2}{\partial x_2}\right)_{(\tau_0,x_0)} < 0$$

$$\left.\frac{\partial^2 \Phi_2}{\partial x_2^2}\right]_{(\tau_0,x_0)} = \left.\int_0^t \exp\left(\int_u^t \frac{\partial F_2}{\partial x_2} ds\right) \frac{\partial^2 F_2}{\partial x_2^2} \exp\left(\int_0^u \frac{\partial F_2}{\partial x_2} ds\right) du\right]_{(\tau_0,x_0)} < 0$$

and

$$\frac{\partial \Phi_2}{\partial x_2} = \exp \int_0^t \frac{\partial F_2}{\partial x_2} ds > 0.$$

We are therefore led to

$$C > 0$$

Hence,

$$BC < 0$$

if (3.5) holds.

Also,

$$d_0' = 1 - \left.\frac{\partial \Theta_2}{\partial x_2}\frac{\partial \Phi_2}{\partial x_2}\right]_{(\tau_0,x_0)}$$

so that $d_0' = 0$ at $T = T_{\max}$. The solution x_0 is stable if $T < T_{\max}$, and $d_0' > 0$ if $T > T_{\max}$. That is, by Theorem 2 of [8], we may conclude that the system (1.1)–(1.3) has a positive periodic solution which is supercritical if $T > T_{\max}$ and is close to $T_{\max}$. □

4. DISCUSSION AND CONCLUSION

In Figure 1, a numerical simulation of system (1.1)–(1.3) is shown in the case that the conditions in Theorem 3.1 hold. The solution trajectory in the (x_1, x_2)-plane is seen to tend toward the periodic solution where x_1 vanishes while x_2 oscillates periodically. The corresponding time series of x_1 and x_2 in this case are shown in Figure 2. Figure 3 shows a numerical solution of (1.1)–(1.3) in the case where the conditions in Theorem 3.4 hold. The solution trajectory tends toward a positive periodic solution containing impulsive jumps in the state variables x_1 and x_2 every period of $T = 130$ units of time. The time series of x_1 and x_2 exhibiting sustained oscillations are seen in Figure 4.

Our analysis suggests a venue for control of the signal transduction process by adjustment of the frequency $\frac{1}{T}$ of the treatments or the dosages, reflected by the values of p and μ, in order to obtain the desired outcome. Specifically, our analytical conclusions indicate that we may expect sustained oscillations in the inhibiting agent even at the vanishing level of the ligand coupled receptors at a low period of external signals. On the other hand, if the period of impulsive drug treatments is kept at a convenient fixed level, then it is possible to adjust the strength of the impulse p so that $T_{\max}$, solved from equation (3.2), renders the inequality (3.1), or (3.5), true, whichever case is the desirable outcome.

Thus, our work is expected to form a valuable basis for further investigations into how we could better manage and control such a complex signaling system, the proper function of which is crucially connected to human's health and disease.

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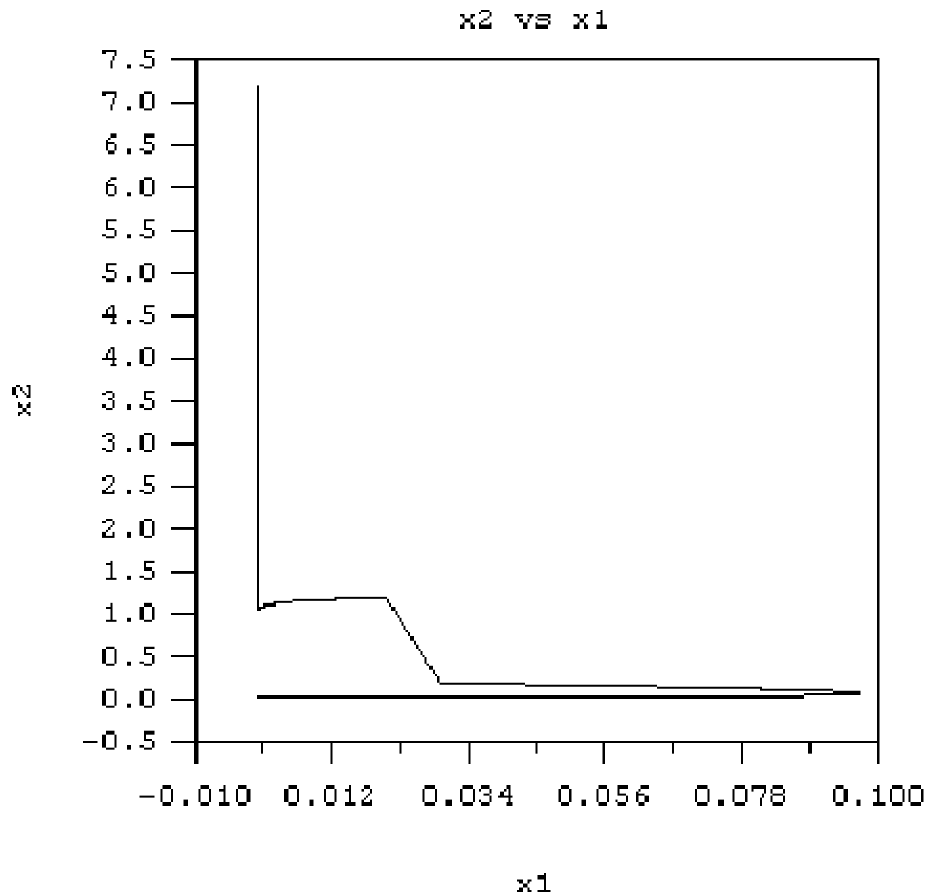

FIGURE 1. Numerical solution of the system (1.1)–(1.2) in the case that $T < T_{\max}$, showing the solution trajectory, in the (x_1, x_2) phase plane, exhibiting sustained oscillation in x_2 at vanishing level of x_1. Here, $a_1 = 0.7, \ldots, b_5 = 0.5$, $\mu = 1$, $p = 0.3$, $T = 5$, and $T_{\max} = 119.6046$.

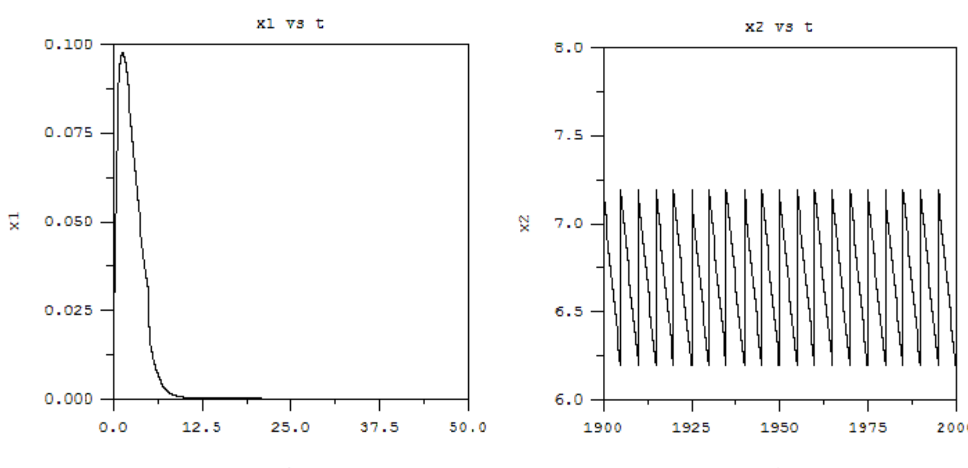

FIGURE 2. The time series of x_1, in 2a), and x_2, in 2b), corresponding to the case seen in Figure 1.

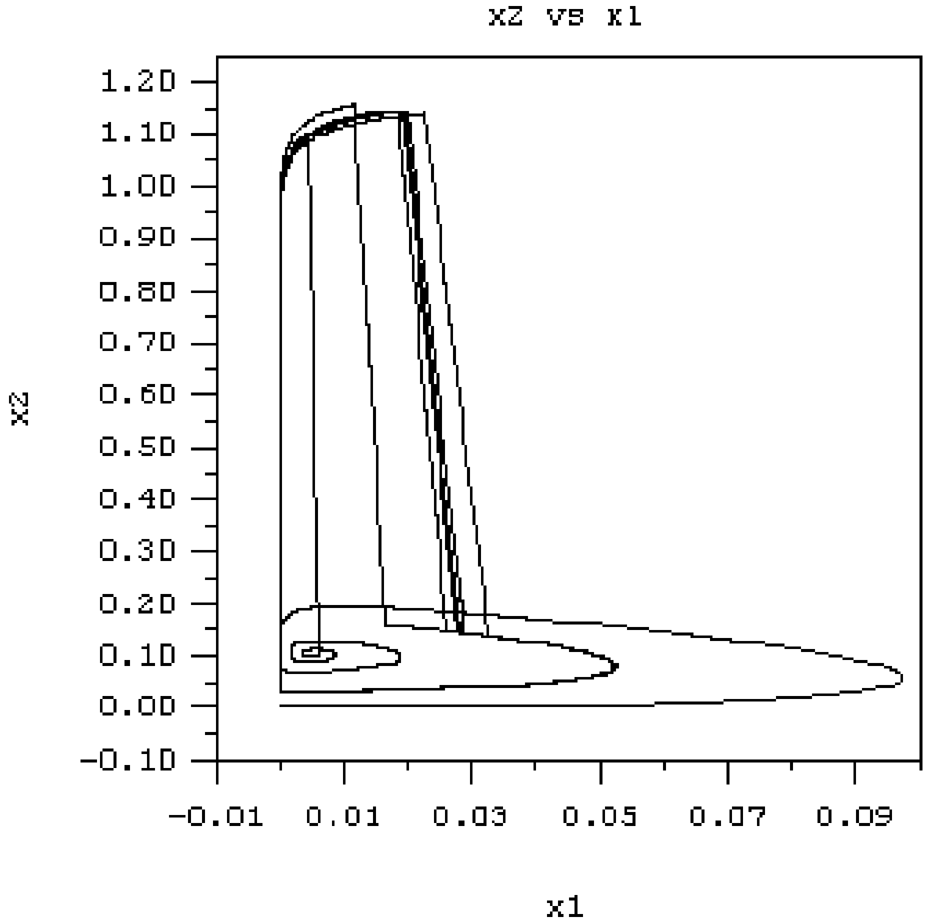

FIGURE 3. Numerical solution of the system (1.1)–(1.2) in the case that $T > T_{\max}$, showing the solution trajectory tending toward a positive periodic solution with impulsive jumps. Here, $a_1 = 0.7, \ldots, b_5 = 0.5$, $\mu = 1$, $p = 0.3$, $T = 130$, and $T_{\max} = 119.6046$.

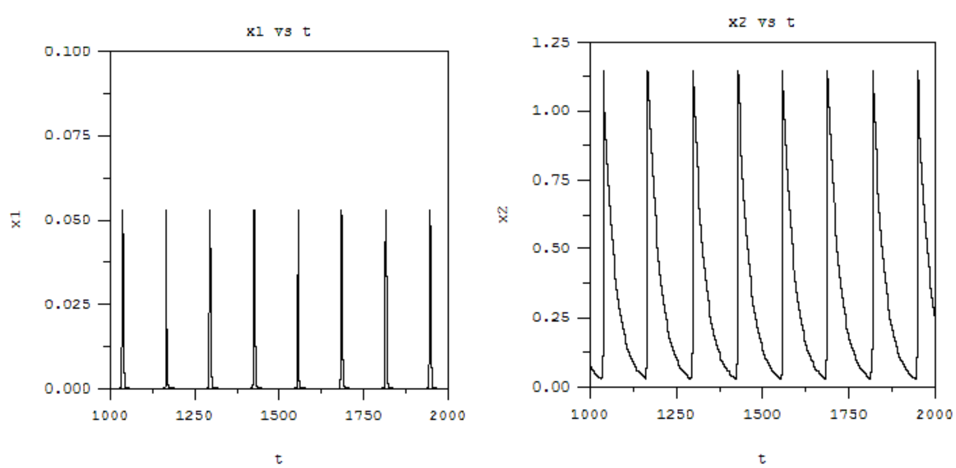

FIGURE 4. The time series of x_1, in 4a), and x_2, in 4b), corresponding to the case seen in Figure 3.